DRAWINGS

Applicants will delay filing of formal drawings until after receipt of the "Notice of Allowability" (PTO-37).

REMARKS

Claims 10-11, 13-15, and 17-21 are pending. All of the claims have been rejected as obvious under 35 U.S.C. § 103(a).

This invention relates to "one-step" immunoassays for extracted analytes which permit efficient extraction of analytes from samples, while minimizing sample manipulation following extraction. See Schwartz Decl. ¶ 9. This permits these assays to be performed by individuals without extensive training in laboratory techniques. Id.

The sample extractions are carried out in a preliminary step in separately provided assay chambers which are not in fluid communication with the sample receiving region of the immunoassay device at the time of extraction. That is, the separately provided assay chamber is physically separated from the lateral flow immunochromatographic device at the time of extraction.

The separation of the assay chamber and lateral flow immunochromatographic device permits greater control over mixing of the sample with the extraction reagents, and the duration of the extraction procedure. This added control over extraction conditions permits greater efficiency of extraction, and increased sensitivity of the assay. Moreover, because the extraction is performed in a separate assay chamber, these assays do not require a complex plastic or cardboard housing or specially designed swabs to fit in the complex housings to help control flow of the sample from

the sample chamber portion of the housing to the sample receiving region of the immunoassay test strip.

35 U.S.C § 103 Rejections

Claims 10-11, 13-15, and 17-21 have been rejected as obvious in view of Imrich et al. (U.S. Patent No. 5,415,994), in view of Hochstrasser (US Patent 4.059,407). Claims 12 and 16 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Imrich et al. in view of Hochstrasser and Bogart et al. (U.S. Patent No. 5,494, 801).

The Claimed Invention

Independent claims 10 and 20 recite the steps of

(b) "providing an assay chamber which is separate from the lateral flow immunochromatographic device,"

(c) "extracting said antigen from said sample . . . in said assay chamber" and

(d) "inserting said sample receiving region [of the immunochromatographic device device] into said assay chamber and contacting said liquid extract."

The Differences Between Imrich, U.S. Patent No. 5,415,994 and the Claimed Invention

The devices in Imrich are described as containing an extraction chamber which is in fluid communication with the immunoassay test strip matrix:

> The devices generally comprise an extraction chamber, a labelling zone having a means for specifically labelling the analyte; and a matrix defining an axial flow path in fluid communication with the extraction chamber, which matrix comprises a sample receiving zone and capture zone located downstream from the sample receiving zone. (col. 2, lines 26-32).

It is clear from the exemplary description above that the extraction chamber in Imrich is in fluid communication with the test strip matrix. Although col. 4, lines 4-6 of Imrich do

describe a stop means, it further notes that the stop means is "to stop ingress of the sample containing support," that is, to keep the swab from touching the immunoassay test strip. At col. 4, lines 24-26, however, Imrich et al. further states that "[t]he extraction chamber is fluidly connected to the matrix by means of an exit port located distally in the chamber." Thus, although the extraction chamber and matrix are in different regions of the Imrich device, they are fluidly connected. Therefore the methods described in Imrich do not include a step of providing an assay chamber which is physically separate from the lateral flow device.

Moreover, Imrich fails to teach inserting the immunochromatographic test strip into the extracted sample tc initiate the assay. In Imrich *et al.* the extraction chamber is in fluid communication with the immunoassay test strip matrix, and the method performed when using the Imrich *et al.* device does not include the step of inserting the sample receiving region of the test strip or housed device into an assay chamber to contact the liquid extract.

In fact, Inrich teaches against the use of a separate preliminary step for extraction of samples, because separate extraction of samples require the user to perform time consuming and expensive "multiple" steps:

> This typically requires that the assay operator place the sample in acid and return later to transfer the acid solution to the assay medium. Multi-step assays such as these require more time and attention from health care personnel and thus are more expensive than one step assays.

Imrich *et al.* at col. 1, lines 61-66. Thus, Imrich teaches that use of a separate sample extraction chamber and later transfer of the extracted sample to the "assay medium" test strip is time consuming and expensive. Finally, Imrich states without qualification that "the present invention provides means by which analytes requiring extraction from

biological samples prior to detection may be extracted and detected in a single step." Imrich, Col. 1, ll. 8-11.

In addition, Imrich describes the immunochromatographic matrix as "contained within a solid casing." Imrich at col. 7, ll. 11-12. Although Imrich describes that the single solid casing can be manufactured in two parts, e.g., by injection molding of top and bottom plastic components, Imrich makes clear that the two components are press-fit together into a single casing after insertion of the matrix into the bottom component. See Imrich at col. 7, ll. 30-49.

In contrast to the methods described in Imrich, the methods claimed in Claims 10-21 of the instant application are directed to methods in which an assay chamber separate from the immunoassay device is provided in which to perform the sample extraction. Moreover, in the methods of claims 10-20, the immunoassay device is inserted into the assay chamber to contact the extracted sample after the preliminary step of sample extraction. During extraction the extraction chamber is not in fluid communication with the assay chamber prior to insertion into the assay chamber. Nothing in Imrich teaches performing the extraction in a separate step, or prying apart the press-fit components of the single casing to remove the test strip matrix for insertion into a sample extraction chamber.

The Differences Between Hochstrasser, U.S. Patent No. 4,059,407 and the Claimed Invention.

Hochstrasser does not describe a lateral flow one-step immunochromatographic device in which the assay is initiated by immersing the sample receiving region into an extracted sample. Instead, Hochstrasser describes a disposable chemical indicator for

the detection of various chemical or biochemical reagents, using a method in which the disposable chemical indicator is completely immersed into the sample or additional reagents in order to detect a specified chemical or biochemical substance. Col. 2, ll. 43-57. Hochstrasser does indicate that antibody may be used as a titrant on the indicator such that exposure to a biological fluid containing analyte will render the titrant unable to react with subsequent indicator labeled antigen. Hochstrasser at col. 7, l. 52-col. 8, l. 20. However, this method does not involve lateral flow, and also requires immersions in at least two solutions (the analyte solution and the labeled antigen solution). Hochstrasser therefore fails to describe a one-step lateral flow immunoassay for the detection of analyte. See Id. Moreover, Hochstrasser further fails to describe the immersion of only a region of the chemical indicator into an extracted sample, which permits a decrease in the volume of sample needed to perform the assay. The lateral flow in the claimed invention permits greater assay sensitivity.

The Federal Circuit Has Recently Made Clear the Stringent Evidentiary Showing Required to Combine References to Render an Invention Obvious

In In re Lee, the Federal Circuit recently made clear the stringent evidentiary burden required for the PTO to make a *prima facie* showing of obviousness based on the combination of elements found in multiple references. In Re Lee, 277 F.3d 1338, 1343, 61 USPQ2d 1430 (Fed. Cir. 2002) (citing cases requiring specific, particular findings as to why a skilled artisan, without knowledge of the claimed invention, would have selected the components for combination to obtain the claimed invention); accord Chemical Separation Tech. Inc. v. United States, 63 U.S.P.Q.2d (BNA) 1114, 1137 (U.S. Ct. Fed. Cls. 2002).

In view of the requirement set forth in In re Lee, Applicants respectfully disagree that the Examiner has made a sufficient evidentiary showing that one of skill in the art would have been motivated to combine Imrich *et al.* with Hochstrasser to obtain the claimed invention.

The Examiner has cited In re Keller, 642 F.2d 413, 208 U.S.P.Q. (BNA) 871 (CCPA 1981) and In re Merck, 800 F.2d 1091, 231 U.S.P.Q. (BNA) 375 (Fed. Cir. 1986) for the proposition that applicants cannot demonstrate nonobviousness by attacking references individually where the rejections are based on combinations of references. 7/30/02 Office Action at 3. However, rather than attacking references individually that the Examiner seeks to combine to render the claimed invention obvious, Applicants instead respectfully point to elements of the invention that are missing from the cited art, and respectfully assert that the showing required by In re Lee for motivation to combine references has not been made.

Indeed, a discussion of the differences between the claimed invention and the prior art is appropriate and necessary for an analysis of obviousness under Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (1966). See In re Lee, 61 U.S.P.Q.2d (BNA) at 1433. Moreover, the Federal Circuit further noted in Lee that that the factual findings to support a combining references for a finding of obviousness must be specific, and thorough:

> "The factual inquiry whether to combine references must be thorough and searching." *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with.

In re Lee, 61 U.S.P.Q.2d (BNA) at 1433 (quoting McGinley v. Franklin Spoirts, Inc., 262 F.3d 1339, 1351-52, 60 U.S.P.Q.2d (BNA) 1001, 1008 (Fed. Cir. 2001), and citing some

of the myriad decisions requiring specific evidence of the motivation to combine references).

"[P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." In re Kotzab, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d (BNA) 1313, 1317 (Fed. Cir. 2000), cited in In re Lee, 61 U.S.P.Q.2d (BNA) at 1433. Thus, there must be some reason for combining elements other than hindsight reconstruction. In re Lee, 61 U.S.P.Q.2d (BNA) at 1434 (holding that neither the examiner nor the Board adequately support4ed the selection and combination of the two cited references to render the claimed invention obvious). Thus, although the Federal Circuit noted in Interconnect Planning Corp. v. Feil, 227 U.S.P.Q. (BNA) 543 (Fed. Cir. 1985) that the claimed invention and references must each be evaluated as a whole, the Federal Circuit concluded that the district court had improperly reconstructed the claimed invention from separate components in the prior art:

> From its discussion of the prior art it appears to us that the court, guided by the defendants, treated each reference as teaching one or more of the specific components for use in the Feil system, although the Feil system did not then exist. Thus the court reconstructed the Feil system, using the blueprint of the Feil claims. As is well established, this is legal error. Id. at 548.
> Furthermore, an invention is not unpatentable because it was "obvious to try." In re O'Farrell, 853 F.2d 894, 902, 7 U.S.P.Q. (BNA) 337 (Fed. Cir. 1988).

There Is No Evidence of Motivation to Combine Imrich et al. with Hochstrasser

Applicants respectfully assert that none of the claims are made obvious by Imrich et al. in view of Hochstrasser et al. First, Hochstrasser is not in the analogous field of lateral flow one-step immunoassays. Instead, Hochstrasser is directed to a chemical indicator which requires multiple immersions in at least two different solutions in order to

carry out a method to detect analyte in a sample. See Hochstrasser at col. 7, l. 45 to col. 8, l. 20. These immersions are not carried out to initiate lateral, flow, but rather, are made to contact a titrant on the chemical indicator with samples and/or reagents. See id. Thus, one of ordinary skill in the art would not have been motivated to combine the chemical indicator of Hochstrasser with the encased lateral flow immunoassay test strip in Imrich. See Teleflex Inc. v. Ficosa North America Corp., 63 U.S.P.Q.2d (BNA) 1374, 1387 (Fed. Cir. 2002) (holding that jury's finding of validity supported because no evidence of the required motivation to combine references, and references not clearly from analogous arts).

Second, because Hochstrasser does not discuss lateral flow immunoassays, it contains absolutely no suggestion to specifically immerse the sample receiving region of a one-step immunochromatographic test strip matrix into an extracted sample, in order to initiate lateral flow. Absent any evidence of a specific motivation to combine the chemical indicator in Hochstrasser with the one-step immunochromatographic device in Imrich, there is no *prima facie* showing of obviousness to overcome. See In re Lee, 61 U.S.P.Q.2d (BNA) at 1435 (holding that the Board could not rely alone on common knowledge and common sense, where there was no specific evidence or reasoned findings of the motivation to combine elements in references); In re Kotzab, 55 U.S.P.Q.2d (BNA) at 1318 ("there was no finding as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of Kotzab's invention to make the combination in the manner claimed.").

Moreover, because the focus of Imrich is a one-step immunochromatographic assay using a device with the sample extraction chamber and test strip housed in a

single casing, there is no motivation to pry apart the two components of the Imrich casing to remove the test matrix for immersion in an extracted sample.

In response to the Applicants arguments that the convenience afforded by Imrich's combination of the sample chamber and test strip into a single housing would have taught away from immersing the test matrix into a separate chamber following extraction, the Examiner suggests that it would have been routine for one of skill in the art to immerse a device with a support member, and plurality of zones into an extracted sample. Office Action mailed 7/30/02 at page 5.

Applicants respectfully disagree, however, that even if one of skill in the art could have carried out the procedure as described by the Examiner, that one of skill in the art would have had any motivation to do so, absent the teachings of the instant application.

It is improper to use hindsight reconstruction to suggest combining two references when neither reference suggests, or provides any motivation for carrying out a lateral flow immunochromatographic assay in which the sample is extracted in a chamber which is not physically housed in a single casing with the immunochromatographic test strip, and where the lateral flow is initiated after sample extraction by immersing the test strip into the extracted sample. See, e.g., In re Kotzab, 55 U.S.P.Q.2d (BNA) at 1318 ("In this case, the Examiner and the Board fell into the hindsight trap.").

Imrich et al. Teaches Away from the Claimed Invention

The Examiner does not appear to disagree that Imrich teaches that a device having the extraction chamber and test strip housed in a single casing is advantageous. 7/30/02 Office action at 5; Imrich at Col. 2, Summary of Invention and at col. 7, ll. 10-41.

Although the Examiner suggests that "Imrich et al., teach a component that contains two plastic removable pieces, the top piece contains the sample-processing feature and the bottom piece is used for strip placement," Imrich does not describe the separation of the top and bottom "components" during methods of using the device to perform the immunoassay. In fact, in order to gain access to the test strip within the single casing, one of skill in the art would have to pry apart the two press-fitted components of the casing, and remove the test strip.

Imrich further teaches against the use of separate extraction of samples, because separate extraction of samples require the user to perform "multiple" steps:

> This typically requires that the assay operator place the sample in acid and return later to transfer the acid solution to the assay medium. Multi-step assays such as these require more time and attention from health care personnel and thus are more expensive than one step assays.

Imrich *et al.* at col. 1, lines 61-66 (emphasis added). Thus, in distinguishing other assays, Imrich teaches that use of a separate sample extraction chamber and later transfer of the extracted sample to the "assay medium" test strip is time consuming and expensive.

Finally, Imrich states that "the present invention provides means by which analytes requiring extraction from biological samples prior to detection may be extracted and detected in a single step." Imrich, Col. 1, ll. 8-11 (emphasis added). One of skill in the art would therefore not have been motivated by Imrich to carry out sample extraction in a separate container, and to wait, or return later to perform the second step of inserting the test strip into the extracted sample.

Accordingly, Imrich describes only the use of devices containing both the immunoassay test strip and an extraction chamber fluidly connected with the test strip.

Imrich does not explicitly describe or suggest a method for detecting a Strep A antigen where the assay chamber is separately provided from the immunoassay device and the immunoassay test strip is inserted into the extracted sample in another step to initiate lateral flow through the test strip.

The Examiner also suggests that because the claimed invention does not limit the size of the housing, arguments relating to distinctions based on Imrich's housing are not persuasive. 7/30/02 Office Action at 5. However, Applicants respectfully assert that by looking to Applicant's claimed invention, the Examiner is improperly using hindsight reconstruction to determine obviousness. The proper analysis is not whether a test strip in a housing might be used in the claimed method, but whether one of skill in the art would have been motivated to use a test strip contained in a housing or casing to perform the claimed method. Because of Imrich's emphasis on the advantages of Imrich's device containing a sample extraction chamber and a test strip in a single casing, to permit one-step extraction and detection, one of skill in the art would not have been motivated to use the device of Imrich to carry out the lateral flow immunochromatographic assays of the claimed invention. Additionally, one of skill in the art would have recognized that the size of the extracted sample needed to immerse the encased Imrich test strip in the extracted sample would have been larger, resulting in dilution of the sample and decreased sensitivity.

Although Imrich does note that the device may be constructed from two plastic components, col. 7, ll. 37-41, Imrich further notes that "[t]he top and bottom components are constructed so that a press fit secures the assembly." Imrich also described that "Injection molding . . . may be used to build plastic parts forming the solid casing."

Imrich at col. 7, ll. 30-32 (emphasis added). One of skill in the art reading the disclosure in Imrich would have understood that after the immunochromatographic test strip is placed in the bottom "component," the "two" components are "press fit" together to form a single solid casing, and that the "two" components which form the casing can then only be separated by undoing the press-fitting. It would have therefore been understood by one of skill in the art that when the Imrich device was in use, the two components were designed to form a single casing, and, in fact, could not easily or conveniently be separated. Imrich thus fails to contain a specific suggestion of the use of an immunoassay test strip lacking a housing which can easily be inserted into a separate assay chamber after extraction—in fact, one would have had to pry apart the press-fitted components of the single Imrich casing in order to gain access to the test strip within.

In contrast, in the claimed device, spatial separation of the separate assay chamber and lack of fluid communication between the assay chamber and the separate lateral flow immunochromatographic assay test strip permits greater control over the length and efficiency of extraction, and the sensitivity of the assay. For example, as noted at page 63 of the specification, a device within the scope of the claimed invention is able to detect Streptococcus cells when present at a concentration as low as 4×10^5 per swab, while the one-step Quidel device can detect Streptococcus cells only when present at a concentration of 8×10^5 cells/swab. In addition, in a study comparing the sensitivity of the OSOM™ Strep A test with the sensitivity of the Quidel QuickVue™ Strep A test, Dr. Richard H. Schwartz determined that the OSOM™ Strep A test had an overall sensitivity of 95%, while the QuickVue™ Strep A test had an overall sensitivity of

87%. Declaration of Richard H. Schwartz at ¶ 3; Schwartz submitted with preliminary amendment, Richard H., Pediatric Infectious Disease J., 16(11):1099-1100 (November 1997), Exhibit 2 to the Declaration of Richard H. Schwartz. Moreover, the commercial success of the OSOM™ Strep A test also establishes that claim 21, specifying that the assay detects as low as 4 X 10^5 cells/sample, is not obvious in view of Imrich.

The Examiner does not appear to dispute that the features of the claimed invention provide greater sensitivity. This increase in sensitivity observed with the OSOM™ Strep A test is the direct result of providing a separate assay chamber and then inserting the the immunochromatographic device into the assay chamber to initiate lateral flow through the immunochromatographic device, rather than having the extraction chamber in flow communication with the sample receiving region of the immunoassay test strip. Thus, the commercial success of the OSOM product is directly related to the claimed features of the invention which require "providing an assay chamber which his separate from the lateral flow immunochromatographic device," and the need for "inserting said sample receiving region of said lateral flow immunochromatographic device into said assay chamber and contacting said liquid extract" thereby permitting more efficient extraction. (See Declaration of Richard H. Schwartz at ¶ 4). A finding of non-obviousness is proper where there is evidence of commercial success of a product, having as a critical feature the claimed invention. Perkin-Elmer Corp. v. ComputerVision Corp., 732 F.2d 888, 221 USPQ 669 (Fed. Cir.), cert. denied, 469 U.S. 857)1994.

Moreover, other immunoassays in use prior to these one-step assays required further manipulation of the sample, such as pipetting or pouring, following extraction of

the sample. (Declaration of Richard H. Schwartz at ¶ 6). This introduced additional sources of error into the test and required performance of the test by more qualified personnel. (Declaration of Richard H. Schwartz at ¶ 6).

As discussed above, Imrich teaches away from using a separate extraction procedure requiring the user to return later to initiate flow through the immunochromatographic device. See Imrich at col. 1., lines 61-66.

In addition, because other references describe one-step methods using devices with unwieldy plastic housings unlikely to fit within a sample chamber small enough to obtain efficient extraction, it is not obvious in view of that art to provide a separate sample chamber and insert the immunoassay device into the sample chamber to initiate the assay.

Applicants therefore respectfully assert that claims 11, 13-15 or 17-21 are not obvious in light of Imrich et al. in combination with Hochstrasser.

Claims 12 and 16 Are Not Made Obvious by Imrich, Hochstrasser and Bogart

Taken together, Imrich, Hochstrasser and Bogart do not teach a method for determining the presence or absence of a Streptococcus antigen, where separate immunoassay devices and an extraction chamber are provided, where the extraction solution comprises 0.2-5M sodium nitrite and 0.02-2M acetic acid, or where the solution contains a color indicator to indicate proper preparation. As discussed above, Imrich fails to teach or suggest a method for the detection of an analyte where the immunoassay test strip is not in flow communication with the extraction chamber. In addition, as noted at page 10 of the Office action mailed 9/2/98, Imrich does not teach

vigorous mixing of the swab and extraction reagents for at least 10 seconds, or an extraction solution where the addition of 0.3 M acetic acid to a color-indicator spiked 2 M sodium nitrite solution changes the color of the final extraction solution. Instead, Imrich teaches that its devices can be used to extract and detect in a single step.

Applicants therefore respectfully assert that neither claims 12 and 16, nor claims 11, 13-15 or 17-21 are obvious in light of Imrich et al. in combination with Hochstrasser and/or Bogart.

CONCLUSION

For the reasons set forth above, Applicants believe that claims 10-21 clearly state that the claimed invention is directed to a method for detecting a Streptococcus antigen where an immunoassay device, and a separate assay chamber are provided. The claims also clearly state that the immunoassay device is inserted into the assay chamber after completion of extraction of the sample. Moreover, Applicants respectfully assert that the claims are not made obvious by Imrich et al., which describes only methods using devices in which the immunoassay test strip is in flow communication with the extraction chamber, and the assay is performed in one-step. Applicants thus believe that the claims are in condition for allowance. If any additional questions regarding the allowability of the claims remain, please contact Applicants representative, Vicki G. Norton, at (858) 720-2570.

Respectfully submitted,

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By: Vicki G. Norton

Vicki G. Norton
Reg. No. 40,745

Brobeck, Phleger & Harrison LLP
12390 El Camino Real
San Diego, California 92130-2081
Tel. No.: (858) 720-2500
Fax No.: (858) 720-2555